# Cancer risk following appendectomy for acute appendicitis (Denmark)

Lene Mellemkjær, Christoffer Johansen, Martha S. Linet, Gloria Gridley, and Jørgen H. Olsen

*Objective*: Epidemiologic studies have not been able definitely to exclude that appendectomy carries a cancer risk. This study was conducted to clarify whether appendectomy is associated with a subsequent increase in cancer risk, since appendectomy is frequently an elective procedure.

*Methods*: The present study included more than 82,000 persons who underwent appendectomy for acute appendicitis during 1977-89 according to the nation-wide Danish Hospital Discharge Register. During a follow-up interval of up to 17 years, cancer incidence was assessed by linkage to the Danish Cancer Registry and compared with the incidence in the general population of Denmark.

*Results*: The total number of malignancies among appendectomized persons was 1.05 times higher than expected with 95 percent confidence intervals of 0.99-1.11. There was no clear significant excess of any specific cancer type.

*Conclusion*: During a postsurgery period of nearly two decades, results of our study did not support the hypothesis that either appendectomy or acute appendicitis are likely to be associated with malignant neoplasms. *Cancer Causes and Control* 1998, 9, 183-187

## Introduction

The appendix is generally considered a vestigial organ. However, in 1964, McVay[1] published a study showing that appendectomized patients had an increased risk for colon cancer. Since then, a large number of case-control studies have presented inconsistent results; about half of the studies have shown a positive association to one or more cancer sites (colon, rectum, stomach, lung, breast, ovary, leukemia, and lymphoma),[2-7] while the others have shown no association to just about the same variety of cancer types.[8-15] Two follow-up studies[16,17] reported no increase in the overall risk for cancer among 1,779 and 28,618 appendectomized patients, respectively.

One hypothesis for a potential association between appendectomy and cancer is that removal of immuno-competent tissue could lead to an increased cancer incidence locally (colon cancer), specifically (non-Hodgkin's lymphoma), or generally (all cancer sites). It also has been hypothesized that a low fiber diet is a common risk factor for both appendicitis and colon cancer.[18] The question of whether the appendix has any importance for cancer development is important considering the high frequency of this procedure, 230 per 100,000 persons each year in Denmark.[19] The majority of appendectomies are carried out to treat acute appendicitis,

but the number of incidental appendectomies is also considerable, especially in connection with gynecologic procedures among women. The present investigation assessed quantitatively risk of cancer by following more than 82,000 Danish patients subsequent to appendectomy for acute appendicitis during a period of up to 17 years through linkage to the nationwide Danish Cancer Registry.

## Materials and methods

The Danish Hospital Discharge Register (HDR) is a centralized register that keeps information on nearly all hospitalizations in Denmark. Each hospitalization results in a record that includes the personal identification number of the individual (encodes gender and date of birth), hospital number, dates of admission and discharge, surgical codes for all operations carried out during the hospitalization (Danish Classification of Surgical Procedures and Therapies)[20] and disease diagnoses (Danish modified version of ICD-8).[21] From the HDR, we identified 82,803 persons discharged with the surgical code for appendectomy and the diagnostic code for acute appendicitis during 1977-89 and who were less than 65 years old at appendectomy.

Dates of death for deceased persons in the appendectomy cohort were obtained from the Death Register file.[22] Cancer occurrence was determined through linkage to the Danish Cancer Registry that lists all cases of cancer, benign neoplasms of the central nervous system, and papillomas of the urinary tract diagnosed in Denmark since 1943.[23]

Entry date was the first day of the month following registration of appendectomy and exit date was either the 65th birthday, date of death, or 31 December 1993, whichever occurred first. We excluded the first year of follow-up, including 211 patients who died, and 435 who turned age 65 during this period; thus, 82,157 persons contributed person-years to the study. The first year of follow-up was excluded to avoid including malignant neoplasms presenting as acute appendicitis.[24,25] Because diagnoses of appendicitis and malignant neoplasms may be less accurate among older persons, all patients who were appendectomized at the age of 65 or older were excluded from the study group and follow-up ended at this age.

The number of cancers observed during follow-up was compared with the expected number calculated from accumulated person-years and gender-specific national cancer incidence rates divided into five-year age and calendar time intervals. In the calculation of incidence rates, multiple primary cancers are counted for an individual; therefore, we also allowed study subjects to have more than one primary cancer during follow-up, and no exclusion was made of subjects who had a cancer diagnosis

prior to appendectomy. The standardized incidence ratio (SIR) – the ratio of observed to expected number of cancers – and corresponding 95 percent confidence intervals (CI) were calculated using Byar's approximation or exact Poisson limits under the assumption that the observed number of cancers in a specific category follow a Poisson distribution.[26]

## Results

A total of 44,379 (54 percent) men and 37,778 (46 percent) women underwent appendectomy for acute appendicitis under the age of 65 years and were followed for more than one year. The mean follow-up from appendectomy was 10.2 years (range of one to 17 years). Of the 757,862 person-years accrued in total during follow-up, 144,755 (19 percent) person-years were collected after 10 or more years of follow-up. There were 43,630 (53 percent) persons who were under age 20 years at appendectomy; 25,780 (31 percent) were 20 to 39 years and 12,747 (16 percent) were 40 to 64 years. Only 696 (one percent) patients had acute appendicitis as a secondary diagnosis, and 48,852 (59 percent) patients had not been hospitalized prior to the admission for appendectomy.

We observed 1,209 cases of cancer compared with 1,149 expected among patients undergoing appendectomy for appendicitis, which yields an SIR of 1.05 (CI = 0.99-1.11) (Table 1). The risks for cancer of the stomach, cancer of other and unspecified female organs (six cases of vulva cancer, one case of vaginal cancer, and one case of cancer in *labium majus*), and cancer of the bladder were borderline significantly increased, and only for metastases and unspecified sites there was a clear significant excess. The observed number of colon cancers was as expected, while the risk for non-Hodgkin's lymphoma was slightly, nonsignificantly increased. The overall cancer risk was increased moderately during the period 10 to 17 years after appendectomy with an SIR of 1.16 (CI = 1.03-1.29), mainly due to excesses of breast cancer and bladder cancer (Table 1). In addition, the risk for metastases and unspecified sites remained elevated during follow-up of more than 10 years.

There were 24 metastases for which the site of the primary tumor was unknown. Of these, six were located to peritoneum, three to bones, five to the brain, three to lymph nodes, and the rest to various sites. The morphology of the metastases differed widely. The site of the primary tumor was also unknown for another 16 cases not coded as metastases but as tumors of unspecified site.

The excess of non-Hodgkin's lymphoma was similar among men and women and during all follow-up intervals (Table 2). For patients appendectomized at under 20 years of age, there was a tendency towards a higher risk compared with patients in older age groups, although the risks

**Table 1.** Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIR) for cancer among patients less than 65 years of age appendectomized for acute appendicitis; first year of follow-up excluded; Denmark

| Cancer site[a] | Follow-up 1-17 years | | | | Follow-up 10+ years | | | |
|---|---|---|---|---|---|---|---|---|
| | Obs | Exp | SIR | (CI)[b] | Obs | Exp | SIR | (CI)[b] |
| All malignant neoplasms (140-205) | 1,209 | 1,149.2 | 1.05 | (0.99-1.11) | 317 | 273.8 | 1.16 | (1.03-1.29) |
| Buccal cavity and pharynx (140-148) | 27 | 26.7 | 1.0 | (0.7-1.5) | 7 | 6.6 | 1.1 | (0.4-2.2) |
| Esophagus (150) | 7 | 8.3 | 0.8 | (0.3-1.7) | 3 | 2.1 | 1.4 | (0.3-4.1) |
| Stomach (151) | 31 | 20.6 | 1.5 | (1.0-2.1) | 6 | 4.5 | 1.3 | (0.5-2.9) |
| Small intestine (152) | 3 | 2.3 | 1.3 | (0.3-3.9) | 0 | 0.5 | — | (0.0-7.2) |
| Colon (153) | 53 | 53.9 | 1.0 | (0.7-1.3) | 13 | 12.5 | 1.0 | (0.6-1.8) |
| Rectum (154) | 26 | 32.6 | 0.8 | (0.5-1.2) | 8 | 7.4 | 1.1 | (0.5-2.1) |
| Liver (155.0) | 7 | 7.2 | 1.0 | (0.4-2.0) | 0 | 1.6 | — | (0.0-2.3) |
| Gall bladder and bile duct (155.1) | 7 | 5.1 | 1.4 | (0.6-2.8) | 2 | 1.1 | 1.9 | (0.2-6.7) |
| Pancreas (157) | 23 | 18.7 | 1.2 | (0.8-1.9) | 9 | 4.2 | 2.2 | (1.0-4.1) |
| Lung (162) | 115 | 114.4 | 1.0 | (0.8-1.2) | 31 | 25.5 | 1.2 | (0.8-1.7) |
| Breast (170) | 156 | 160.1 | 1.0 | (0.8-1.1) | 53 | 39.1 | 1.4 | (1.0-1.8) |
| Cervix uteri (171) | 49 | 47.3 | 1.0 | (0.8-1.4) | 17 | 11.8 | 1.5 | (0.8-2.3) |
| Corpus uteri (172) | 32 | 26.2 | 1.2 | (0.8-1.7) | 4 | 5.1 | 0.8 | (0.2-2.0) |
| Ovary (175) | 26 | 31.0 | 0.8 | (0.6-1.2) | 3 | 6.8 | 0.4 | (0.1-1.3) |
| Other and unspecified female organs (176) | 8[c] | 3.5 | 2.3 | (1.0-4.5) | 1 | 0.8 | 1.3 | (0.0-7.1) |
| Prostate (177) | 15 | 17.4 | 0.9 | (0.5-1.4) | 5 | 4.0 | 1.2 | (0.4-2.9) |
| Testis (178) | 54 | 54.3 | 1.0 | (0.8-1.3) | 12 | 14.0 | 0.9 | (0.4-1.5) |
| Kidney (180) | 19 | 24.9 | 0.8 | (0.5-1.2) | 6 | 5.6 | 1.1 | (0.4-2.3) |
| Urinary bladder (181) | 61 | 46.3 | 1.3 | (1.0-1.7) | 20 | 10.8 | 1.9 | (1.1-2.9) |
| Melanoma (190) | 50 | 58.3 | 0.9 | (0.6-1.1) | 16 | 15.2 | 1.1 | (0.6-1.7) |
| Non-melanoma skin (191) | 168 | 152.6 | 1.1 | (0.9-1.3) | 41 | 40.0 | 1.0 | (0.7-1.4) |
| Brain and nervous system (193) | 77 | 65.5 | 1.2 | (0.9-1.5) | 14 | 15.3 | 0.9 | (0.5-1.5) |
| Non-Hodgkin's lymphoma (200, 202, 205) | 40 | 33.4 | 1.2 | (0.9-1.6) | 10 | 8.3 | 1.2 | (0.6-2.2) |
| Hodgkin's disease (201) | 18 | 21.2 | 0.9 | (0.5-1.3) | 5 | 4.9 | 1.0 | (0.3-2.4) |
| Multiple myeloma (203) | 8 | 7.5 | 1.1 | (0.5-2.1) | 0 | 1.8 | — | (0.0-2.0) |
| Leukemia (204) | 28 | 28.5 | 1.0 | (0.7-1.4) | 5 | 5.5 | 0.9 | (0.3-2.1) |
| Other specified sites (156, 158-61, 162.2, 163, 164, 173, 174, 179, 192, 194-197) | 61 | 59.2 | 1.0 | (0.8-1.3) | 15 | 13.4 | 1.1 | (0.6-1.9) |
| Metastases and unspecified sites (198-199) | 40 | 22.4 | 1.8 | (1.3-2.4) | 11 | 5.4 | 2.0 | (1.0-3.6) |

[a] Storm HH, Pihl J, Michelsen E, Nielsen A. *Cancer Incidence in Denmark 1993.* Copenhagen, Denmark: Danish Cancer Society, 1996.
[b] CI = 95% confidence interval.
[c] Six cases of vulva cancer (three melanomas, one liposarcoma, one squamous cell carcinoma, and one case with no histologic confirmation), one case of cancer in vagina and one case of cancer in *labium majus.*

were not significantly different (*P* = 0.1). There was no difference between risk estimates for nodal and extranodal lymphomas. Six cases of lymphomas in digestive organs were observed (one stomach, one ileum, one descending colon, two liver, and one retroperitoneum) *cf* 3.4 expected.

## Discussion

Similar to the results of two previous follow-up studies,[16,17] we found no convincing evidence of an association between appendectomy and cancer. Our study is population-based and included the largest number of appendectomized patients followed up to date. The available data provided an opportunity to explore the long-term effects of appendectomy, with a maximum time-interval between surgery and end of follow-up of 17 years. Still, it may be argued that a full evaluation of cancer risk demands an even longer follow-up of perhaps 30 to 40 years or more. Our slightly elevated risk estimate for all cancer sites for follow-up of more than 10 years underlines the need for a reevaluation of cancer incidence in the present cohort in some years.

We did not include persons who underwent appendectomy for reasons other than acute appendicitis, including malignant neoplasms, because other underlying diseases are likely to affect these patients' cancer risk. However, restriction of the study group to those with acute appendicitis meant that we could not distinguish between the

**Table 2.** Observed (Obs) and expected (Exp) number and standardized incidence ratios (SIR) for non-Hodgkin's lymphoma among patients appendectomized for acute appendicitis according to different cohort characteristics and topography of the lymphoma, first year of follow-up excluded; Denmark

| | Person-years | Obs | Exp | SIR | (CI)[a] |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 410,423 | 26 | 21.7 | 1.2 | (0.8-1.8) |
| Female | 347,439 | 14 | 11.7 | 1.2 | (0.7-2.0) |
| Years from appendectomy | | | | | |
| 1-4 | 321,241 | 14 | 11.9 | 1.2 | (0.6-2.0) |
| 5-9 | 291,866 | 16 | 13.2 | 1.2 | (0.7-2.0) |
| 10+ | 144,755 | 10 | 8.3 | 1.2 | (0.6-2.2) |
| Age at appendectomy (yrs) | | | | | |
| 0-19 | 419,887 | 13 | 6.6 | 2.0 | (1.0-3.4) |
| 20-39 | 244,334 | 10 | 12.1 | 0.8 | (0.4-1.5) |
| 40-64 | 93,641 | 17 | 14.7 | 1.2 | (0.7-1.9) |
| Appendicitis diagnosis[b] | | | | | |
| Primary | 751,742 | 40 | 33.1 | 1.2 | (0.9-1.7) |
| Secondary | 6,120 | 0 | 0.3 | — | (0.0-11.9) |
| Appendectomy[c] | | | | | |
| At first admission | 501,890 | 30 | 21.9 | 1.4 | (0.9-2.0) |
| Not at first admission | 255,971 | 10 | 11.5 | 0.9 | (0.4-1.6) |
| Topography of lymphoma | 757,862 | | | | |
| Nodal | | 31 | 25.2 | 1.2 | (0.8-1.7) |
| Extranodal | | 9 | 7.8 | 1.2 | (0.5-2.2) |
| Stomach | | 1 | 1.5 | 0.7 | (0.0-3.8) |
| Other digestive organs | | 5 | 1.9 | 2.7 | (0.9-6.2) |
| Brain | | 1 | 0.8 | 1.2 | (0.0-6.9) |
| Unknown | | 0 | 0.3 | — | (0.0-11.6) |

[a] CI = 95% confidence interval.
[b] According to the hospital discharge records.
[c] Does not= 757,862 due to rounding.

effect of appendicitis and the effect of appendectomy on cancer risk. Misclassification of acute appendicitis may occur, because discharge diagnoses may be allocated before histologic confirmation is obtained. This affects the interpretation of risk estimates for appendicitis, which may be underestimated, but does not affect the interpretation of risk estimates for appendectomy.

Colon cancer was of interest, *a priori*, in part due to a number of studies demonstrating a positive association with appendectomy,[1-3] but our study clearly shows no relationship between appendectomy for acute appendicitis and colon cancer. Thus, our investigation provides no support to the hypothesis that there is a common risk factor for both appendicitis and colon cancer.

Even though the excess of non-Hodgkin's lymphoma was modest and nonsignificant, the finding is intriguing because appendectomy involves removal of lymphoid tissue. However, a previous case-control study of non-Hodgkin's lymphoma showed no relationship with appendectomy, and no significant excesses of non-Hodgkin's lymphoma have been seen subsequent to removal of lymphoid tissue from other anatomic sites,

such as tonsillectomy or splenectomy.[8,27] Further, it does not seem very plausible that removal of the appendix should have any carcinogenic effect since the lymphatic tissue of the appendix resembles Peyer's patches, found abundantly in the distal half of ileum.[28] Also, there seemed to be no anatomically proximate consequence of appendectomy since the observed number of gastrointestinal lymphomas was quite similar to that expected. Other subanalyses for non-Hodgkin's lymphoma, such as stratification on gender, follow-up intervals, and other characteristics showed no particular risk pattern. In our opinion, the weak association between appendectomy and non-Hodgkin's lymphoma found in the present study is most likely a chance finding.

We have no obvious explanation for the excess of cases with unknown site of the primary tumor. Indeed, this seems strange considering that all of these cases occurred in subjects under the age of 65 years. Our best suggestion would be that the undiagnosed primary tumor or metastasis somehow gave rise to symptoms mimicking acute appendicitis, although we would then have expected the excess to occur within a few years from the appendicitis

hospitalization, whereas the excess actually remained 10 or more years after this event. The increased risks for cancer of the stomach and cancer of other and unspecified female organs during total follow-up, and for bladder cancer and breast cancer during late follow-up were quite moderate, and there is no particular support from earlier studies for these findings.

Our investigation provides evidence that appendectomy for acute appendicitis is not linked to any apparent increase in cancer incidence. Confidence limits for risk estimates were quite narrow, thus excluding an overall cancer risk elevation greater than 11 percent. In conclusion, during the first 17 years following surgical excision of the appendix, this event seems to be unrelated to cancer development, and acute appendicitis and malignant neoplasms do not seem to share underlying risk factors.

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